UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/820,647	04/07/2004	Kevin Liu	K0003-201-US	8504

51625 7590 06/10/2009

GLOBAL PATENT GROUP - KAL
10411 Clayton Road, Suite 304
St. Louis, MO 63131

EXAMINER	
RAO, DEEPAK R	

ART UNIT	PAPER NUMBER
1624	

NOTIFICATION DATE	DELIVERY MODE
06/10/2009	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

lhall@globalpatentgroup.com
knhall@globalpatentgroup.com
salgrillo@globalpatentgroup.com

UNITED STATES PATENT AND TRADEMARK OFFICE

Commissioner for Patents
United States Patent and Trademark Office
P.O. Box 1450
Alexandria, VA 22313-1450
www.uspto.gov

BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 10/820,647
Filing Date: April 07, 2004
Appellant(s): LIU ET AL.

Dennis A. Bennett

For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed March 9, 2009 appealing from the Office action mailed October 4, 2007.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The examiner is not aware of any related appeals, interferences, or judicial proceedings which will directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal.

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

The appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The appellant's statement of the grounds of rejection to be reviewed on appeal is correct.

(7) Claims Appendix

The copy of the appealed claims contained in the Appendix to the brief is correct.

(8) Evidence Relied Upon

1. Vippagunta et al., Crystalline Solids, Advanced Drug Delivery Reviews, 48, pp. 3-26, 2001.
2. West, Solid Solutions, Solid State Chemistry and its applications, pp. 358 & 365, 1988.
3. Ulrich, Chapter 4: Crystallization, Kirk-Othmer Encyclopedia of Chemical Technology, August 2002.
4. Bundagaard, Design of Prodrugs: Introduction, page 1, 1985.
5. Silverman, Prodrugs and Drug Delivery Systems, The Organic Chemistry of Drug Design and Drug Action, pp. 352-400, 1992.
6. Fayer et al., PubMed Abstract (J. Clin. Pharmacol. 41(3):305-16) 2001.
7. Peterson et al., Expanding the scope of Crystal from evaluation in Pharmaceutical Science, J Pharm Pharmaceutical Sci, 9(3), pp. 317-326, 2006.

(9) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claims:

1. Claims 1-13, 18-36, 41-49, 51-56, 59-64 and 66-69 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a compound of Formula I or a pharmaceutically acceptable N-oxide or salt thereof, does not reasonably provide enablement for a pharmaceutically acceptable **prodrug**, **metabolite**, **ester**, **amide** or **solvate** thereof. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

In evaluating the enablement question, several factors are to be considered. Note *In re Wands*, 8 USPQ2d 1400 and *Ex parte Forman*, 230 USPQ 546. The factors include: 1) The nature of the invention, 2) the state of the prior art, 3) the predictability or lack thereof in the art, 4) the amount of direction or guidance present, 5) the presence or absence of working examples, 6) the breadth of the claims, and 7) the quantity of experimentation needed.

The instant claim recites "A compound ... or a .... pharmaceutically acceptable prodrug, pharmaceutically active metabolite, ... pharmaceutically acceptable ester, pharmaceutically acceptable amide, or pharmaceutically acceptable solvate thereof" wherein there is insufficient description in the specification regarding the types of 'prodrugs, metabolites, esters, amides and solvates' intended by the recitation. The specification at page 27 provides a definition for the term "prodrug", however, does not provide any explanation of the terms 'pharmaceutically active metabolite or pharmaceutically acceptable solvate' of the compounds of Formula I. The term 'prodrug' generally known to represent 'a physiologically functional derivative, for example, an

ester or an amide, which upon administration to a mammal is capable of providing (directly or indirectly) a compound of the invention or an active metabolite thereof'. In the instant case, however, the specification does not provide what are some of the examples of "derivatives" intended by the terms 'prodrugs, metabolites, esters, amides' etc..

The term 'prodrug' and/or 'metabolite' is directed to esters and amides of compounds of Formula I. However, the definition of various substituent groups in Formula I already include such groups, i.e., acids, esters, amides, etc. The specification does not provide what other 'compounds' of the invention are intended to be the above referred "prodrugs" and "metabolites". The generic formula of the claims already include both esters and the corresponding free acid forms, see e.g., see the term " $-C(O)OR_4$", wherein R_4 is independently H, alkyl, etc. There is no disclosure regarding any other esters or amides that are capable of providing compounds of the invention. Further, specification does not provide sufficient explanation of the term "metabolite". A metabolite is any compound which is pharmaceutically active *in vivo* when it undergoes "metabolic" process and the specification does not provide any disclosure of what these compounds might be that *in vivo* transform in to the instantly claimed compounds. The specification does not provide what other 'compounds' of the invention are intended to be metabolites. Since functional groups such as esters, amides, etc. are already included in the claimed compounds, it is not clear whether compounds bearing these groups are excluded from being a potential "pharmaceutically acceptable **prodrug**, **metabolite**, **ester**, **amide** or **solvate**" of the claimed invention. If compounds bearing these groups (i.e., ester, etc.), which are likely to undergo *in vivo* transformation, are excluded then what is included in the

definition of the above term and where on the structural Formula I are these groups placed; the specification does not provide any direction to one of ordinary skill in the art.

A prodrug as defined by Bundgaard (Design of Prodrugs) "is an inactive species, and therefore, once its job is completed, intact prodrug represents unavailable drug" (see page 1). Thus, an important requirement of prodrugs is that they be pharmacologically inactive. The scope of the term 'prodrugs' is quite broad. A state of the art reference, Silverman (The Organic Chemistry of Drug Design and Drug Action) teaches many strategies for making prodrugs. Among them are polymer-bound prodrugs (pages 369-374), acyclic prodrugs which form heterocyclic compounds *in vivo* (page 360), conjugates consisting of two or more drug molecules which are cleaved into active drug molecules (page 377), amine precursors which are converted to amines *in vivo* (page 358), and drugs bound to a carrier via a linker (page 374). Applicant has neither described nor provided working examples for the combination of the invention compound with various types of 'other compounds' or 'pharmaceutical excipients' intended by the instant claim language. In a clinical trial setting, it would require undue experimentation to determine whether a particular compound meets the criteria of a 'prodrug'.

Further, the specification has no working examples of "solvate" of compound of Formula I; and some of the exemplified compounds within the claimed genus were in contact with solvent. Yet they have not formed solvate as evident form spectral data provided for these compounds.

Searching the pertinent art in the related pyrimidine area did not result in support for such solvates of instant pyrimidine compounds. Searching the more general area of solvates resulted

in pertinent reference West applied below. West clearly shows lack of predictability of the art in the solvate area.

Based on these two facts, a scope of enablement rejection follows using relevant Wands factors. Hence, the burden of establishing the *prime facie* case is met with.

(i). **The nature of the invention and the state of the prior art:**

Specification is not adequately enabled as to how to make solvate of compounds of Formula I Specification has no example of solvate of the instant compounds. Specification neither defines the term nor provides an enabling disclosure of 'solvates' of the instant compounds.

The compound of Formula I embrace substituted pyrimidine compounds substituted with variable groups R_1, R_3, etc. Careful calculation of the number of compounds embraced in the instant Formula I shows a large number of compounds and there is no teaching of any solvate of this large genus.

Search in the pertinent art, including water as solvent resulted in a pertinent reference, which is indicative of unpredictability of solvate formation in general. The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Thus, in the absence of experimentation one cannot predict if a particular

solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. Compared with polymorphs, there is an additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate. In the instant case of solvate a similar reasoning therefore apply. Water is a solvent and hence it is held that a pertinent detail of West, which relates to solvates, is also applicable to water.

In addition, an additional search resulted in Vippagunta et al., Advanced Drug Delivery Reviews 48: 3-26, 2001, which clearly states that formation of solvates in unpredictable. See entire document especially page 18, right column section 3.4. Note Vippagunta et al., states "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds".

Joachim Ulrich (Kirk-Othmer Encyclopedia of Chemical Technology) provides that "Pseudopolymorphs are solvates or in the case of water as solvent, hydrates, which means crystals that incorporate solvent molecules into the crystal lattice. Pseudopolymorphs exhibit different crystal forms and/or different densities, solubilities, dissolution rates, colors, hardnesses, etc. Compared with polymorphs, there is an additional degree of freedom (than temperature and pressure), which means a different solvent or even the moisture of the air that might change the stabile region of the pseudopolymorph".

(ii). **The predictability or lack thereof in the art:**

Hence the solvate as applied to the above-mentioned compounds claimed by the applicant are not art-recognized compounds and hence there should be adequate enabling disclosure in the specification with working example(s).

(iii). **The amount of direction or guidance present:**

Examples illustrated in the experimental section are limited to making the compounds not related to solvates. There is no example of solvate of instant compound. Many of the exemplified compounds were shown in the specification that have come in contact with water and/or other solvent but there is showing that these compounds formed solvates. Hence it is clear that merely bringing the compound and water or solvent together does not result in solvate and additional direction or guidance is needed to make them - specification has no such direction or guidance.

(iv). **The presence or absence of working examples:**

There is no working example of any solvate formed. The claims are drawn to solvate, yet the numerous examples presented all failed to produce a solvate or even solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 "[T]he specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there, is no evidence that such compounds exist... the examples of the patent do not produce the postulated compounds... there is ... no evidence that such compounds even exist." The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, there should be showing supporting that solvates of these compounds exists and therefore can be made.

(v). **The breadth of the claims & the quantity of experimentation needed:**

Specification provides no support, as noted above, for compounds generically embraced in the claim 1 would lead to desired solvate of the compound of Formula (I). As noted above,

the genus embraces a large number of compounds and hence the claims are extremely broad. The quantity of experimentation needed would be an undue burden on skilled art in the chemical art since there is inadequate guidance given to the skilled artisan for the many reasons stated above. Even with the undue burden of experimentation, there is no guarantee that one would get the product of desired **solvate** of compound of Formula I embraced in the instant claims in view of the pertinent reference teachings.

2. Claims 51-57 and 59-65 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for treatment of diabetes, does not reasonably provide enablement for a method of modulating a peroxisome proliferators-activated receptor (PPAR) function; a method of inhibiting the formation of adipocytes in a mammal; a method of treating a disease generally; a method of treating a PPAR-modulated disease or condition or a metabolic disorder generally. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The specification fails to enable one skilled in the art to use the claimed compounds. The use disclosed in the specification is as PPAR regulators, useful as hypoglycemic agents, etc., see page 1. Test assays to measure PPAR binding activity are provided at pages 21-22, however, no results are provided for any of the exemplified compounds. The data provided in the specification is insufficient such that no reasonable extrapolation could be made by one skilled in the art regarding the activity of the instantly claimed compounds. This area of receptor activity is highly structure specific and unpredictable as can be seen from the range of the results

obtained for the tested compounds. Further, there is no evidence on record which demonstrates that the *in-vitro* screening tests relied upon are recognized in the art as being reasonably predictive of success in any of the contemplated areas of regulating PPAR. Such a reasonable correlation is necessary to demonstrate such utilities. See *Ex parte Stevens*, 16 USPQ 2d 1379 (BPAI 1990); *Ex parte Busse et al.*, 1 USPQ 2d 1908 (BPAI 1986) (the evidence must be accepted as "showing" such utility, and not "warranting further study"). Fayer et al. (PubMed abstract) report that such correlation or lack thereof is important to predict drug-drug interactions. This clearly highlights the unpredictability in the art and the need for undue experimentation. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the claimed compounds as PPAR regulators.

The instant claims 51-52 recite "a method of modulating a PPAR function" wherein the term "modulating" generally encompasses blocking, activating, partial blocking and partial activating. However, the compounds were not shown to have all these properties. For example, it is revolutionary for a compound to be effective as a blocker, activator and partial blocker/activator. The specification did not provide any competent tests or data to establish that the compounds have the claimed 'calcium sensing receptor modulating activity'. The remaining claims recite 'a method of inhibiting the formation of adipocytes'' 'a method of treating a disease comprising identifying a patient in need thereof'; etc. The instant claims appear to be 'reach through' claims. Reach through claims, in general have a format drawn to mechanistic,

receptor binding or enzymatic functionality and thereby reach through to the corresponding therapeutic method of any or all diseases, disorders or conditions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

Claims are drawn to a method for treatment of 'a PPAR-modulated disease or condition' and the specification provides a select list of disorders such as diabetes, hyperinsulinemia, atherosclerosis, etc. However, the instant claim includes disorders that are known to exist and those that may be discovered in the future and therefore, is extremely broad. For example, atherosclerosis is a common form of arteriosclerosis associated with the formation of atheromas which are deposits of yellow plaques containing cholesterol, lipids, and lipophages within the intima and inner media of arteries. This results in a narrowing of the arteries, which reduces the blood and oxygen flow to the heart and brain as well as to other parts of the body and can lead to a heart attack, stroke, or loss of function or gangrene of other tissues.

(Only a few of the claimed diseases are discussed here to make the point of an insufficient disclosure, it does not definitely mean that the other diseases meet the enablement requirements).

In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the instantly claimed methods.

(10) Response to Argument

1. Claims 1-13, 18-36, 41-49, 51-56, 59-64 and 66-69, drawn to the preparation and/or use of pharmaceutically acceptable prodrugs, metabolites, esters, amides, and solvates of compounds of Formula I are not enabled:

Appellant's arguments have been fully considered but they were not deemed to be persuasive. Appellant argues that 'specific working examples of prodrugs of Formula I are not required to satisfy 35 U.S.C. 112, first paragraph'. Specification has no working example of a prodrug, metabolite or solvate of a compound of the various structural formulae of the instant claims. For example, some of the exemplified compounds within the claimed genus were in contact with solvent. Yet they have not formed solvate as evident form spectral data provided for these compounds. Applicant's arguments have been fully considered but they were not deemed to be persuasive. Applicant argues that 'a patent need not disclose what is well known in the art'.

MPEP 2164.03 provides the relationship of predictability of the art and the enablement requirement (portion of MPEP is provided below for convenience):

> **2164.03 [R-2] Relationship of Predictability of the Art and the Enablement Requirement**
>
> The amount of guidance or direction needed to enable the invention is inversely related to the amount of knowledge in the state of the art as well as the predictability in the art. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). The "amount of guidance or direction" refers to that information in the application, as originally filed, that teaches exactly how to make or use the invention. The more that is known in the prior art about the nature of the invention, how to make, and how to use the invention, and the more predictable the art is, the less information needs to be explicitly stated in the specification.
> **In contrast, if little is known in the prior art about the nature of the invention and the art is unpredictable, the specification would need more detail as to how to make and use the invention in order to be enabling.** >See, e.g., *Chiron Corp. v. Genentech Inc.*, 363 F.3d 1247, 1254, 70 USPQ2d 1321, 1326 (Fed. Cir. 2004) ("Nascent technology, however, must be enabled with a specific and useful teaching.' The law requires an enabling disclosure for nascent technology because a person of ordinary skill in the art has little or no knowledge independent from the patentee's instruction. Thus, the public's end of the bargain struck by the patent system is a full enabling disclosure of the claimed technology." (citations omitted)).<

> **The "predictability or lack thereof" in the art refers to the ability of one skilled in the art to extrapolate the disclosed or known results to the claimed invention.** If one skilled in the art can readily anticipate the effect of a change within the subject matter to which the claimed invention pertains, then there is predictability in the art. On the other hand, **if one skilled in the art cannot readily anticipate the effect of a change within the subject matter to which that claimed invention pertains, then there is lack of predictability in the art**. Accordingly, what is known in the art provides evidence as to the question of predictability. In particular, the court in *In re Marzocchi*, 439 F.2d 220, 223-24, 169 USPQ 367, 369-70 (CCPA 1971), stated:
>
> > **[I]n the field of chemistry generally, there may be times when the well-known unpredictability of chemical reactions will alone be enough to create a reasonable doubt as to the accuracy of a particular broad statement put forward as enabling support for a claim.** This will especially be the case where the statement is, on its face, contrary to generally accepted scientific principles. Most often, additional factors, such as the teachings in pertinent references, will be available to substantiate any doubts that the asserted scope of objective enablement is in fact commensurate with the scope of protection sought and to support any demands based thereon for proof. [Footnote omitted.]
>
> The scope of the required enablement varies inversely with the degree of predictability involved, but even in unpredictable arts, a disclosure of every operable species is not required. A single embodiment may provide broad enablement in cases involving predictable factors, such as mechanical or electrical elements. *In re Vickers*, 141 F.2d 522, 526-27, 61 USPQ 122, 127 (CCPA 1944); *In re Cook*, 439 F.2d 730, 734, 169 USPQ 298, 301 (CCPA 1971). However, **in applications directed to inventions in arts where the results are unpredictable, the disclosure of a single species usually does not provide an adequate basis to support generic claims**. *In re Soll*, 97 F.2d 623, 624, 38 USPQ 189, 191 (CCPA 1938). In cases involving unpredictable factors, such as most chemical reactions and physiological activity, more may be required. *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970) (contrasting mechanical and electrical elements with chemical reactions and physiological activity). See also *In re Wright*, 999 F.2d 1557, 1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); *In re Vaeck*, 947 F.2d 488, 496, 20 USPQ2d 1438, 1445 (Fed. Cir. 1991). **This is because it is not obvious from the disclosure of one species, what other species will work.**

As explained before, the specification or the state of the art provides all possible 'prodrug', 'metabolite', 'ester', 'amide' or 'solvate' forms of the compounds of Formula I. MPEP 2164.04 requires that - 'a reasonable basis to question the enablement of the claimed invention must be provided'. This was done by discussing state of the art references Bundgaard, West, Vippagunta, Ulrich, etc. (copies provided with the previous office action). Particularly, MPEP section provides:

> While the analysis and conclusion of a lack of enablement are based on the factors discussed in MPEP § 2164.01(a) and the evidence as a whole, it is not necessary to discuss each factor in the written enablement rejection. The language should focus on those factors, reasons, and evidence that lead the examiner to conclude that the specification fails to teach how to make and use the

claimed invention without undue experimentation, or that the scope of any enablement provided to one skilled in the art is not commensurate with the scope of protection sought by the claims.

Appellant indicates with regards to 'prodrug', 'ester' and 'amide' that 'specific working examples are not required to satisfy 35 USC 112, first paragraph'. With respect to 'metabolite', applicant argues that 'a person having ordinary skill in the art would recognize the pharmaceutically active metabolites of compounds of formula (I)'. However, there is no description of any such prodrugs or metabolites of the compound or a method of preparation of the same. The specification does not provide any explanation regarding how the instantly recited characteristic of a metabolite is established. There is neither a procedure describing how such metabolites are prepared nor examples that illustrate the recited activity. Further, the instant claims appear to be 'reach through' claims. Reach through claims, in general have a format drawn to a characteristic or functionality of the compound or composition and thereby reach through to all types of compositions, for which they lack written description and enabling disclosure in the specification thereby requiring undue experimentation for one of skill in the art to practice the invention.

The state of the references provide the unpredictable nature pertinent to the scope of the instant claims, see e.g., West: "it is not usually possible to predict whether solid solutions will form, or if they do form what is the compositional extent". Vippagunta: "Each solid compound responds uniquely to the possible formation of solvates or hydrates and hence generalizations cannot be made for series of related compounds". The state of the art, as reflected in the prior art cited above, does not support Appellant's position that only routine experimentation would be

necessary to practice the full scope of the claims, i.e., prepare all types of prodrugs, metabolites, solvates, etc. of the compounds of Formula I.

Generally, 'solvate' is formed by the association or combination of a solute unit with solvent molecules which association may involve physical or chemical forces or both and may vary in degree from a loose, indefinite complex to the formation of a distinct chemical compound. Another state of the art reference, Peterson et al. (J Pharm Pharmaceut Sci 2006) provides 'solvate' as a type of crystal form of pharmaceutical compounds (see page 317). The reference further provides the challenges associated with the design of crystalline materials that include one or more solvent/water molecules in the crystal lattice. "By extension, and just as the exact function of a protein and quantitative parameters of activity are not predictable from primary and secondary structure, the prediction of crystal properties is not possible in the absence of structural information and measurements"; "even when chemically compatible functional groups are present it is not possible to accurately predict if a co-crystal, a eutectic mixture or simply a physical mixture will result from any given experiment" (see page 320, col. 2). "There remain several limitations to the applications of what is currently known to the design of useful materials. As mentioned earlier, it remains intractable to reliably predict crystal structure. Multi-component crystals are well out of reach for prediction due in part to complex energetic landscapes, lack of appropriate charge density models and a large number of degrees of freedom, making computation unfeasible" (see page 322, col. 1). The reference further identifies 'the challenges faced by pharmaceutical scientists' as: "(i) to understand the requirement of a particular compound in terms of materials structure and properties, and (ii) to creatively integrate crystal engineering within the limits of pharmaceutical acceptability of components to obtain

new forms of active ingredients with desirable properties for formulation and delivery" (see page 322, col. 2).

As per the collective discussion provided in the previous and present office actions, it is established that the fact situation based on the disclosure and the state of the art references, fails to teach how to make and use the instant invention commensurate in scope of the claims, without undue experimentation.

2. Claims 51-57 and 59-65 draw to methods of modulation of PPAR; or methods to treatment of PPAR mediated diseases are not enabled under 35 U.S.C. 112, first paragraph.

Appellant argues that 'exemplified compounds were evaluated in a cell-based assay to determine their human PPAR activity and results are disclosed on pages 48-51 of the specification' and 'because the PPAR binding activity can be determined through routine experimentation, a person having skill in the art has no need to be able to predict activity based on structure in order to practice the claimed invention'. However, as clearly indicated in the rejection above, the unpredictability of therapeutic approach related to many of the diseases encompassed by the instant claims and applicant did not provide any explanation as to how treatment of all types of PPAR induced diseases is enabled. Further, one skilled in the art recognizes that there are complex interactions between individual genetic, developmental state, sex, dietary, environmental, drug, and lifestyle factors that contribute to various disease states, making it even more challenging to have a single therapeutic agent for the treatment of diverse diseases induced by PPAR.

Appellant's arguments with regards to claims reciting 'method of treating PPAR-

modulated diseases' and 'a method of treating a disease selected from the group consisting of obesity, diabetes, ... and hypertoxic lung injury' have been fully considered but they were not deemed to be persuasive. Appellant argues that 'the specification is enabling with respect to the preparation of pharmaceutically acceptable prodrugs, metabolites, esters, amides and solvates; a method of modulating a PPAR function; a method of treating a PPAR-modulated disease; etc.'. However, the biological data in pages 48-51 provides a range of EC_{50} data for the instant compounds with respect to PPAR-binding activity and there is nothing in the specification how this data extrapolates to the treatment of all types of specific diseases, e.g., metabolic disorders, etc. of the instant claims. Appellant did not state on record or provide any guidance that the assays provided are correlated to the clinical efficacy of the treatment of various disorders encompassed by the claims. As can be seen from specification, the *in vitro* biological data holds significant role in determining the dosage regimen based on the minimal effective concentration of each of the compound to achieve the desired activity.

Fayer et al. (PubMed abstract) report 'the lack of correlation between the in vitro inhibition by a PPAR-gamma agonist and its effects on the clinical pharmacokinetics' and conclude that there is "need to recognize factors other than plasma drug concentrations and potency of in vitro enzyme inhibition when extrapolating in vitro data to predict in vivo drug-drug interactions". This clearly highlights the unpredictability in the art and the need for undue experimentation. The evidence of record does not disclose any known compounds of similar structure, which have been demonstrated effective in modulating PPAR function generally; or in treating all types of PPAR-modulated diseases. The state of the art, as reflected in the prior art cited above, does not support Appellant's position that only routine experimentation would be

necessary to practice the full scope of the claims 51-57 and 59-65.

Rigorously planned and executed clinical trials, incorporating measurement of appropriate biomarkers and pharmacodynamic endpoints are critical for selecting the optimal dose and schedule for treatment of any particular disease. A detailed understanding of the molecular mode of action of the PPAR alongside the elucidation of the molecular pathology of individual disease is required to identify the disease symptoms and individual patients that may benefit most from treatment. It is also important to construct a pharmacologic audit trail linking molecular biomarkers and pharmacokinetic and pharmacodynamic parameters for each individual disease therapeutic intervention. Undue experimentation would be necessary to use all the generic compounds recited in claim 1 to modulate PPAR function generally or to treat all PPAR-modulated diseases with the large genus of compounds of formula I.

There is no evidence of record, which would enable the skilled artisan in the identification of the patient that is in need of the instantly claimed therapeutic activity. In view of the breadth of the claims, the chemical nature of the invention, the unpredictability of ligand-receptor interactions in general, and the lack of working examples regarding the activity of the claimed compounds, one having ordinary skill in the art would have to undergo an undue amount of experimentation to use the claimed compounds for the treatment of the diverse disorders instantly claimed.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

/Deepak Rao/
Primary Examiner,
Art Unit 1624

Conferees:

1. /James O. Wilson/

   Mr. James O. Wilson
   Supervisory Patent Examiner
   Art Unit 1624

2. /Joseph K. McKane/

   Mr. Joseph K. McKane
   Supervisory Patent Examiner
   Art Unit 1626